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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,517	08/01/2001	Michael F. Clarke	060173-0014 (UMIP-003)	6988

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,517	CLARKE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-14,18-24,27-30,32-35,38,40,187,188,194 and 198-205* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-14,18-24,27-30,32-35,38,40,187,188,194 and 198-205* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed on 1/26/04 has been entered. Claims 2, 3, 5, 25, 26, 31, 39, 41-183, 185, 186, 196, 197 have been canceled by this amendment. Claims 1, 4, 23, 32 have been amended. Claims 199-205 are newly submitted. Currently, claims 1, 4, 6-14, 18-24, 27-30, 32-35, 38, 40, 187, 188, 194, 198-205 are under examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 1/26/04 response would be addressed to the extent that they apply to current rejection.

Claim Objections

Claims 1, 23, and 32 are objected to because "a" before "LINEAGE" should be replaced with "the" ((claim 1(d), claim 23 (e), claim 32 (b))).

Claims 7, 24, 33 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In this case, the previous claims (1, 23, 32) have been limited to solid tumors of epithelial origin by the amendment, whereas dependent claims (7, 24, 33) recite, "wherein the solid tumor is a sarcoma". According to Stedman's medical dictionary, a sarcoma refers to tumors originated from the connective tissue, not epithelial tissue. Further, the limitation

"epithelial cancer" has been presented in the base claims 1, 23, 32 (solid tumors of epithelial origin). Thus, the dependent claims fail to further limit the subject matter of a previous claim.

Claim 23 is objected to because of the following informalities: Claim 23 is marked as "presently presented", and the correct format should be "currently amended" (See the Revised Amendment Practice of 37 CFR 1.121, OG Notice 23 September 2003)

Claim 32 is objected to because the word "stem" should be inserted after "tumor" in step (c), line 4 as presented in page 6 of 1/26/04 submission.

Claim 34 is objected to because "lectin" does not appear to specifically binds to the CD markers recited in the amended base claim (32).

Claims 187 and 198 are objected to because they are duplications of claims 6 and 194 respectively. Applicant is advised that should claims 6 and 194 be found allowable, claims 187 and 198 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 200 is objected to because a space should be inserted between "claim" and the number "1".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 6, 7, 9-14, 18-22, 32-35, 38, 40, 187, 188, 199-203 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because the amended claim 1 recites, "said isolated tumor stem cell is at least 75% free from other cells", which implies that a single cell may be divided and 25% of the cell may contain other cells. This is illogical to the common definition of a cell, since it could not be possible that a portion of a single viable cell contains other cells. Thus, the metes and bounds of the claims are unclear. For the purpose of prior art, this limit will not be considered in this Office action.

Claim 1 recites the limitation "said isolated solid tumor stem cell" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 is vague and indefinite because the phrase "that fail the requirements of (b), (c), (d), and (e), below" appears to define "said solid tumor", yet each of the (b), (c), (d), and (e) defines a tumor stem cell. Thus, the metes and bounds of the claims are uncertain.

Claim 32 is vague and indefinite because it recites, "solid tumor stem cell positive marker CD44", whereas "CD44 ANTIGENS ARE THE PRINCIPLE CELL SURFACE RECEPTORS FOR HYALURONATE AND THIS INTERACTION MEDIATES BINDING OF LYMPHOCYTES TO HIGH ENDOTHELIAL VENULES" (Mesh term database, PubMed). Where applicant acts as his or her own

lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "CD44" in claim 32 is used by the claim to mean "solid tumor stem cell positive marker", while the accepted meaning is "the principle cell surface receptors for hyaluronate". The term is indefinite because the specification does not clearly redefine the term. Deleting the phrase "solid tumor stem cell positive marker" would obviate this rejection.

Claims 202 and 203 recite the limitation "the enriched population of claim 22". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

The prior rejection of claims 1-14, 18-30, 32-35, 38-40, 185-188, 194, and 196-198 under 35 U.S.C. 112, 1st paragraph, is withdrawn in view of claim amendment. Claims are now drawn to characterizing tumor stem cells according to a set of specific markers, which has been adequately described in the specification.

ENABLEMENT REQUIREMENT

The prior rejection of claims 1-14, 18-30, 32-35, 38-40, 185-188, 194, and 196-198 under 35 U.S.C. 112, 1st paragraph, is withdrawn in view of claim amendment. Claims are now drawn to identifying tumor stem cells according to a set of specific markers.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 6-8, 18, 20, 21 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Salmon et al* (New Eng J Med 1978;298:1321-7) and as evidenced by *Janeway, Jr. et al* (Immunobiology, 1999) and *Hartman et al* (Int J Cancer 1999;82:256-67). This rejection now applies to new claims 199-201.

The amended and new claims are drawn to an isolated epithelial solid tumor stem cell that is tumorigenic, $CD44^+$, lin^-, and $CD24^{lo}$, and B38.1 and/or ESA positive.

Salmon et al disclose isolated solid epithelial tumor stem cells, i.e. isolated from the ovarian carcinoma, and form colonies in vitro (gave rise to new tumor cells), thus tumorigenic. *Salmon et al* go on to teach that the colony-forming assay correlates well with the in vivo property of STSC, thus is a more reliable criteria than other measures (2nd paragraph, page 1321). Although *Salmon et al* do not teach the recited markers of their tumor stem cells, the Office has shown that the markers describe the inherent

property of an epithelial tumor stem cell, and because the solid epithelial tumor stem cells disclosed by *Salmon et al* are encompassed by the instant claims, i.e. derived from a solid epithelial tumor (ovarian carcinoma), and tumorigenic, therefore, these cells would intrinsically bear $CD44^+$, lin^-, and $CD24^{lo}$, B38.1 and/or ESA. This is because "PRODUCTS OF IDENTICAL CHEMICAL COMPOSITION CAN NOT HAVE MUTUALLY EXCLUSIVE PROPERTIES. A CHEMICAL COMPOSITION AND ITS PROPERTIES ARE INSEPARABLE". THEREFORE, IF THE PRIOR ART TEACHES THE IDENTICAL CHEMICAL STRUCTURE, THE PROPERTIES APPLICANT DISCLOSES AND/OR CLAIMS ARE NECESSARILY PRESENT. *IN RE* SPADA, 911 F.2D 705, 15 USPQ2D 1655, 1658 (FED. CIR. 1990). "[O]NCE A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFT TO THE APPLICANT TO SHOW AN OBVIOUS DIFFERENCE". (MPEP 2112, 2112.01)

Claim 199 is a product-by-process claim. It is noted patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). In the instant case, the markers used in the enrichment process are the inherent surface markers for a solid epithelial tumor stem cell, and because the solid epithelial tumor stem cells disclosed by *Salmon et al* are encompassed by the instant claims, i.e. derived from a solid epithelial tumor (ovarian carcinoma) and tumorigenic, the cells obtained by the method of claim 40 should contain a solid tumor stem cell as taught by *Salmon et al*.

Accordingly, *Salmon et al* anticipate the instant claims, and the rejection stands.

In 1/24/04 response, Applicants respond to the prior art rejection as a whole, which will be addressed below.

Applicants argue that the cited references fail to teach or suggest numerous additional elements found in the independent and dependent claims, including but not limited to levels of isolation (e.g. 75% in claim 1), the presence or absence of the markers, source of the cells, and the ability to form new cells (Remark, 2nd paragraph, page 9).

The amendments and arguments have been fully considered but they are not found persuasive.

As an initial matter, the "75%" limitation in claim 1 has not been considered for reasons discussed under 35 U.S.C. 112, 2nd paragraph. With respect to other recited limitations, *Salmon et al* do teach the source of the cells, i.e. solid tumor stem cells of epithelial origin, and their ability to form new tumor cells *in vitro* and *in vivo*, whereas the surface markers are the intrinsic property of the cells. Thus, the arguments are not persuasive.

Applicants go on to argue while the Examiner has argued that certain cells isolated in the prior art must inherently have one or more of certain of the various markers claimed, applicants disagree with this assertion, and nothing in the cited references teaches or suggest isolated cells having the combination of markers now claimed (1st paragraph & footnote, page 10).

In response, Applicants are reminded that once a reference teaching product appearing to be substantially identical is made the basis of a rejection and the examiner

presents evidence or reasoning tending to show inherency, the burden shift to the applicant to show an obvious difference, and such showing should be factual evidence. Applicants are reminded that the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or inherently possess characteristics of claimed tumor stem cells, which requires *factual evidence* demonstrating that actual, unobvious differences exist (or that the claimed products are functionally different than those taught by the prior art) and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989). These reminders have been indicated in the previous Office action, but applicants fail to provide such factual evidence in their response. Accordingly, for reasons of record and those set forth foregoing, the rejection stands.

Claims 1, 4, 6-8, 18, 20, 22 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Salmon et al* (US 4,411,990, IDS/A1). This rejection now applies to new claims 199-203.

The amended and new claims are drawn to an isolated epithelial solid tumor stem cell that is tumorigenic, $CD44^{+}$, lin^{-}, and $CD24^{lo}$, and B38.1 and/or ESA positive.

Salmon et al teach epithelial tumor stem cells (e.g. table 1, adenocarcinoma of the ovary) that serve as the seeds of metastatic spread of cancer and the colony-forming (column 1, lines 19-36), and thus tumorigenic. Therefore, *Salmon et al* clearly teach an isolated cell that is epithelial origin and tumorigenic, e.g. the cells grown *in vitro* form new tumors when transplanted *in vivo*. Although *Salmon et al* do not teach the markers of the tumor stem cells, the Office has shown that these markers describe the inherent property of an epithelial tumor stem cell, and because the solid tumor stem cells disclosed by *Salmon et al* are encompassed by the instant claims, i.e. derived from a solid epithelial tumor, and tumorigenic, therefore, these cells would intrinsically be $CD44^+$, lin^-, and $CD24^{lo}$ and B38.1 and/or ESA positive.

Claim 199 is a product-by-process claim. It is noted patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). In the instant case, the markers used in the enrichment process are the inherent surface markers for a solid epithelial tumor stem cell, and because the solid epithelial tumor stem cells disclosed by *Salmon et al* are encompassed by the instant claims, the cells obtained by the method of claim 40 should contain a solid tumor stem cell as taught by *Salmon et al*.

Accordingly, the rejection stands.

Applicants presented arguments as a whole to all prior art rejections, which have been addressed in the foregoing *Salmon* reference, thus will not be reiterated.

Claims 1, 4, 6-8, 18, 23, 24, 27-29, 187, 194, 198 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Martin et al* (Exp Hematol 1998;26:252-64), and as evidenced by *Schlom et al* (US 4,612,282), and the rejection now applies to the amended claims 199-201.

The amended and new claims are drawn to an isolated epithelial solid tumor stem cell or an enriched population of solid tumor stem cell that is tumorigenic, $CD44^+$, lin^-, and $CD24^{lo}$, and B38.1 and/or ESA positive.

Martin et al teach isolating metastatic tumor cells from the peripheral blood, hence, these cells have been shown to form new tumor growth *in vivo* (tumorigenic). The primary site of the metastatic tumor cells taught by *Martin et al* is breast cancer, a solid epithelial tumor, thus, *Martin et al* teach a solid epithelial tumor stem cell that is tumorigenic. The term "enrichment" is a relative term, the cells taught by *Martin et al* have been enriched at least 25-fold compared to the original collected tumor cells (abstract), wherein about 4% of the cells in the enriched population express CD44 (section in page 257), therefore, the end cell population would also be enriched for CD44. Although *Martin et al* do not teach other recited markers of the tumor stem cells, the Office has shown that these markers describe the inherent property of an epithelial tumor stem cell, and because the solid tumor stem cells disclosed by *Martin et al* are encompassed by the instant claims and are the same type of tumor as illustrated in the specification, i.e. derived from breast cancer, therefore, these cells would intrinsically be $CD44^+$, lin^-, $CD24^{lo}$ and B38.1 and/or ESA positive.

Claim 199 is a product-by-process claim. It is noted patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). In the instant case, the markers used in the enrichment process are the inherent surface markers for a solid epithelial tumor stem cell, and because the solid epithelial tumor stem cells disclosed by *Martin et al* are encompassed by the instant claims, the cells obtained by the method of claim 40 should contain a solid tumor stem cell as taught by *Martin et al*.

Accordingly, the rejection stands.

Applicants presented arguments to all prior art rejections as a whole, which has been addressed in the first *Salmon* reference, thus will not be reiterated.

Claims 1, 4, 6, 7, 9-13, and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Nierodzik et al* (Blood 1998;92:3694-3700). This rejection now applies to new claims 199-201.

The amended and new claims are drawn to an isolated epithelial solid tumor stem cell that is tumorigenic, $CD44^+$, lin^-, and $CD24^{lo}$, and B38.1 and/or ESA positive.

Nierodzik et al teach epithelial tumor stem cells (e.g. undifferentiated colon carcinoma cells, 5th paragraph of page 3694) and enhanced metastasis of these cells after treatment with thrombin (10-160 fold) (1st paragraph of the article). Although *Nierodzik et al* do not teach the markers of the tumor stem cells, the Office has shown that these markers describe inherent property of an epithelial tumor stem cell, and

because the solid tumor stem cells disclosed by *Nierodzik et al* are encompassed by the instant claims, i.e. derived from a solid epithelial tumor (colon carcinoma), and tumorigenic, therefore, these cells would intrinsically be $CD44^{+}$, lin^{-}, and $CD24^{lo}$ and B38.1 and/or ESA positive.

Claim 199 is a product-by-process claim. It is noted patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). In the instant case, the markers used in the enrichment process are the inherent surface markers for a solid epithelial tumor stem cell, and because the solid epithelial tumor stem cells disclosed by *Nierodzik et al* are encompassed by the instant claims, the cells obtained by the method of claim 40 should contain a solid tumor stem cell as taught by *Nierodzik et al*.

Accordingly, the rejection stands.

Applicants presented arguments as a whole, which has been addressed in the foregoing Salmon reference, thus will not be reiterated.

The prior rejection of claims 1, 3, 4, 6, 9-14, and 18 under 35 U.S.C. 102(b) as being anticipated by *Bromberg et al* (PNAS 1995;92:8205-9) is withdrawn in view of claim amendment because *Bromberg et al* taught a solid tumor stem cell of melanocyte origin, not epithelial cell origin.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23 and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Martin et al* (Exp Hematol 1998;26:252-64), in view of *Salmon et al* (US 4,411,990, IDS/A1), for reasons of record (papers #11 and 14) and set forth above in this action as discussed in detail under 35 U.S.C. 102(b) by *Martin et al.*

Claims 1, 18, and 19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Salmon et al* (US 4,411,990, IDS/A1), in view of *Jeffries et al* (Mol Cell Bio 2000 Jun;20:3928-41), for reasons of record (papers #11 and 14) and set forth above in this rejection as discussed in detail under 35 U.S.C. 102(b) by *Salmon et al* (US 4,411,990, IDS/A1).

In view of claim amendment, Claims 1 and 9-14 are newly rejected under 35 U.S.C. 103(a) 103(a) as being unpatentable over *Salmon et al* (US 4,411,990, IDS/A1), and *Bromberg et al* (PNAS 1995;92:8205-9).

Salmon et al teach epithelial tumor stem cells (e.g. table 1, adenocarcinoma of the ovary) that serve as the seeds of metastatic spread of cancer and the colony

forming, i.e. tumorigenic (column 1, lines 19-36), which intrinsically bear the markers recited in the claims.

Although *Salmon et al* do not teach genetically modifying the solid epithelial tumor stem cells, *Bromberg et al* supplemented *Salmon et al* by providing a new tool, genetically modifying tumor cells, for studying the factors that would influence tumor metastasis. *Bromberg et al* transfected solid melanoma stem cells with a retroviral vector encoding normal or mutant extracellular Tissue Factor, and the metastatic (tumorigenic) ability of these cells were tested in a SCID mice model (e.g. abstract). They go on to teach that this is a different approach compared to the existing one using anti-TF antibody for study, and the method provides further insight as to the pathways involved in the cancer metastasis (2nd paragraph, Introduction). Although *Bromberg et al* do not use a solid tumor stem cell of epithelial origin, the teaching established the state of the art at the time of instant filing, i.e. it is well known in the art that tumor stem cells could be modified by a polynucleotide vector expressing a gene of interest, and a reporter gene, wherein the polynucleotide is integrated into a chromosome of the cell (retroviral vector).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method as taught by *Bromberg et al* by simply substituting the melanoma stem cells with the epithelial tumor stem cells taught by *Salmon et al* for studying the influence of a gene of interest on epithelial tumor stem cell behavior with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the mechanism of

cancer cell metastasis has been the focus of cancer investigation and the gene modification method provides a powerful new tool for the investigation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed. Claims 32-35, 38, 40, 188, 204, and 205 appear to be free of the cited prior art of record, however, they are subject to other rejections and objections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

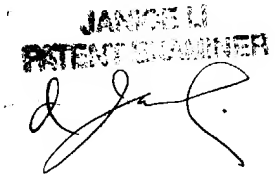
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist **Rena Jones** whose telephone number is **571-272-0571**.



Q. Janice Li
Patent Examiner
Art Unit 1632

QL
April 16, 2004